**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Muriel Moser et al.

Application No.: 10/072,425 Confirmation No.: 4226

Filed: February 7, 2002 Art Unit: 1644

For: DENDRITIC-LIKE CELL/TUMOR CELL HYBRIDS AND HYBRIDOMAS FOR INDUCING AN ANTI-TUMOR RESPONSE Examiner: G. R. Ewoldt

Commissioner for Patents
P.O. Box 1450
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**DECLARATION OF Gordon Macpherson, DPhil., UNDER 37 C.F.R. §1.132**

Sir:

I, **Gordon Macpherson,** hereby declare that:

1. I received a DPhil degree in 1971 from the University of Oxford. I currently hold the position of Reader in Experimental Pathology (retired).

2. My expertise in dendritic cell related immunology stems from more than 35 years in active research concerning dendritic cell life histories, properties and functions. In addition, as Tutor in Medicine at Oriel College, Oxford and Reader in Experimental Pathology in the University of Oxford I have taught widely on all aspects of immunology and pathology, including tumour pathology and immunology. A list of relevant publications on which I am an author is attached to this declaration.

3. I am not an employee of or affiliated with the assignee/owner of the above referenced U.S. Patent application, and do not otherwise possess a financial interest in the above referenced patent application. I am being compensated for the time spent in preparation of this declaration. I respectfully submit that I am qualified to speak and render opinions as to the disclosure in the present application and the state of the art.

4. I have read the Office Action mailed April of 2009, "office action". I understand that the Examiner cited Guo et al. (1988), (referred to herein as Guo et al.) and Sornasse et al. (referred to herein as Sornasse et al.) in the office action.

5. State of the Art at the time of the Invention:
At the time of Applicant's invention, making and using dendritic cell tumor cell fusions capable of activating naïve T cells and inducing a tumor specific immune response in vivo had not been reported. Thus, the field of making and using dendritic cell tumor cell fusions in tumor therapy was at its very infancy, with little, if any guidance, for its development from the prior art.

6. At the time of the invention, there were several methods being attempted to enable dendritic cells to present tumor-associated antigens in order to stimulate anti-tumor immunity. One method was to pulse dendritic cells with exogenous antigens as taught in Sornasse et al. A second method was to pulse dendritic cells with RNA. A third method, proposed by Applicant, was to fuse dendritic cells with tumor cells.

7. At the time of the invention, the concept of presenting tumor associated antigens to the immune system by means of a dendritic cell-tumor cell fusion was not reported in the art to the best of my knowledge.

8. The activated B cell/tumor cell fusions of Guo et al. had been reported. However, these B cell tumor cell fusions reported by Guo et al. did not provide significant guidance to one of skill in the art with respect to the use of dendritic cell tumor cell fusions for initiating an immune response in vivo for several reasons.

9. This result has yet to be reported as being successfully reproduced in mice or humans.

10. It was a surprise that the B cell tumor cell fusions were successful in mounting an anti-tumor response in vivo, and the mechanism of their action is not clear.

11. There is no in vitro data in the paper by Guo et al. that shows that the B cell tumor cell fusions actually initiate the anti-tumor immune response by stimulating naïve T cells. In fact, it is likely that the tumor specific immune response is generated through dendritic cells, not directly through the B cell tumor cell fusions. The rationale is as follows: If tumor cells are injected subcutaneously, typically the tumor would stay localized under the skin. However, the B cell component of the B cell tumor cell fusion provides the fusion with migratory properties, which allow the fused cell to travel to the lymph nodes, where the tumor antigens are incorporated, processed and presented by the dendritic cells of the recipient to T cells in the lymph node, initiating the immune response. The transfer and presentation of antigens expressed on a non-dendritic cell by a dendritic cell is well documented in the literature.

12. The B cell tumor cell fusions taught by Guo are not initiating the tumor response in vivo. In other words, the B cell tumor cell fusions taught by Guo are likely not the cells activating tumor specific, naive T cells in vivo, a distinguishing characteristic of dendritic cells.

13. Further support that the B cell tumor cell fusions taught by Guo are not activating tumor specific, naive T cells in vivo, is the low expression of MHC class II and B7 expressed on their cell surface. Figure 1 of Guo et al. illustrates that the cell surface expression of MHC class II and B7 is much lower on the B cell tumor cell fusions than on the activated B lymphocytes. This low cell surface expression of MHC class II and B7 on the B cell tumor cell fusions indicates their likely inability to activate naive T cells in vivo.

14. At the time of the invention, no-one knew that MHC class II or B7 expression would be regulated differently in activated B cells versus dendritic cells. In view of Guo et al.'s teaching that the B cell-tumor cell hybrids express low levels of MHC Class II antigen relative to activated B lymphocytes, one would have predicted, at the time of the invention, that MHC Class II and B7 expression in the dendritic cell-tumor cell hybrid would also have decreased relative to dendritic cells.

15. At the time of the invention, one would not have known that GM-CSF would be effective in upregulating MHC Class II on dendritic cell-tumor cell fusions.

16. The dendritic cell component of dendritic cell tumor cell fusions is not only structurally distinct from B cell component of the B cell tumor cell fusions taught by Guo, the dendritic cell component processes and presents tumor associated antigens differently from the B cell component. Because of their distinctly different methods of antigen processing and presentation, and the unlikelihood that they are able to activate naïve T cells in vivo, the B cell tumor cell fusions taught by Guo would provide only minimal and only very general guidance at best towards a method of making and using dendritic cell tumor cell fusions in inducing a tumor specific immune response in vivo.

17. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

22 October 2009
Date

Gordon Macpherson, DPhil.